LETTERS TO THE EDITOR

Urea and its bioavailability in newborns

EDITOR,—Jackson suggests that colonic salvage of urea N – that is, its return to the body N pool and contributing to the effective supply of N – is an important component in the handling of urea N in the newborn.¹ Although of interest for nitrogen economy during growth, pregnancy, low protein intake or during hibernation in bears, such an hypothesis, at least in the newborn child, is not based on compelling evidence.

The estimates of urea N salvage are based on incomplete excretion in urine of the total urea synthesised in the body.² The discrepancy could result not only from the hydrolysis of urea in the gut but also from excretion of urea in the skin. A significant proportion of N released from hydrolysis of urea in the gut is also known to be recycled into urea or excreted as ammonia in the breath. In healthy adults with a normal protein intake about 20% of synthesised urea is not excreted in urine, and an insignificant amount of urea N is incorporated into protein.³

Whether such a salvage of N occurs in newborns is not known. Data on breast fed infants, both pre-term and full term, have shown that most of the urea ingested is not bioavailable – that is, it is not hydrolysed in the gut.⁴ Studies in healthy pre-term and full term newborns show that the rate of urea synthesis measured by isotopic tracers ranges between 3 mg and 6 mg N/kg/hour, which is similar to the rate of urinary urea N excretion measured in a number of balance studies.^{5,6} In contrast, Wheeler *et al* observed very high rates of urea N synthesis (about 17.3 mmol N/kg/day or 20 mg N/kg/hour) in six neonates after major abdominal surgery.⁷ However, the rate of urinary urea N excretion was similar to that reported by others. Thus the discrepancy between synthesis and excretion was astronomical (80%). Interestingly, the recycled N was only a small component of urea synthesis. Several concerns can be raised regarding the validity of measurements in their study – route of tracer administration, the catabolic state of the infant, the accuracy of urine collection, etc. All question the conclusion regarding the salvage of urea N in these infants.

Thus published data on newborn babies do not support the concept that 'urea production and salvage appear to be normal features of early infancy'. It may be important only when protein intake is marginal or only in certain animal species.

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- 5 Kalhan SC. Rates of urea synthesis in the human newborn: Effect of maternal diabetes and small for gestational age. *Pediatr Res* 1993; 34: 801–4.
- 6 Battista MA, Price P, Kalhan S. Effect of pediatric parenteral amino acid mixture on leucine and urea kinetics in preterm infants. *Pediatr Res* 1994; 35: 307A.
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Dr Jackson comments:

Dr Kalhan's comments revisit a longstanding controversy which simply underlines the need for good data in a difficult area of investigation. There are three points of importance: whether salvage of urea-nitrogen has functional importance under any circumstance; whether it is important in infancy; and the nature of the importance. We have formally addressed the methodological criticisms raised.¹ Based on an extensive series of investigations we know for adults that normally 25% of daily urea-nitrogen production is salvaged.² In infants and children the major factors which influence the rate of salvage are the overall metabolic demand, determined in part by energy intake, the absolute protein intake relative to the magnitude of the metabolic demand for protein, and the presence of a functional colonic microflora.³

The data indicate that for infancy three phases for urea kinetics can be identified: (i) shortly after birth before the microflora are properly established, little or no salvage; (ii) up to 6 weeks of age, with an established flora, salvage is very high in response to the intense metabolic demand; and (iii) after 6 to 8 weeks of age, when salvage is moderate. For each phase there are clear differences in nitrogen metabolism, as identified by other investigators. These considerations adequately explain the different results obtained by different groups. There is no good reason simply to dismiss the data of Wheeler *et al*,⁴ as we have found considerable salvage in free living infants aged 3 to 6 weeks who were breast fed. These data confirm that at least 50% of the nitrogen salvaged from urea is retained within the system. Although the nature of the retention remains an open question at this point in time, we have early evidence which traces the label into essential amino acids.

Given that growth is an important feature of infancy and that for most people the lowest protein diet they ever take is their mother's milk, the evidence in favour of the importance of urea-nitrogen salvage need not be compelling to justify full consideration of its potential importance.

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Fresh frozen plasma and neonatal sepsis

EDITOR,—Acunas and colleagues conclude that fresh frozen plasma (FFP) is less effective than intravenous immunoglobulin as

adjunctive treatment for neonatal sepsis.¹ They also highlight the possible risk of viral transmission with its use.

FFP may also contain viable donor lymphocytes, exposing the recipient to potentially fatal transfusion associated graft versus host disease (TA-GvHD).² This usually occurs in those with defective cell mediated immunity. However, it may occur in the apparently immunocompetent,³ and preterm infants are also at risk.⁴ Although TA-GvHD may be prevented by irradiation of blood products,³ FFP is not routinely irradiated on most neonatal units and therefore TA-GvHD may be another potential disadvantage of the use of FFP in neonates.

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- 2 Wintergerst U, Meyer U, Remberger K, Belohradsky BH. Graft versus host reaction in an infant with DiGeorge syndrome. *Monatsschr Kinderheilkd* 1989; 137: 345–7.
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- 4 Berger RS, Dixon SL. Fulminant transfusion-associated graft-versus-host disease in a premature infant. *J Am Acad Dermatol* 1989; 20: 945–50.

EMLA and informed consent in neonates

EDITOR,—We were very interested in the account of the use of EMLA cream in 21 neonates,¹ following an earlier trial in seven babies.² There seem to be few direct reports of the safe use of EMLA in newborns, though Koren suggested that EMLA is in widespread unlicensed use in North America for circumcision of neonates, with no apparent harm.³ Use of EMLA is not recommended for babies under 1 year of age in the United Kingdom, but the use of EMLA in infants older than 1 month has recently been approved in the USA.

Neonates may be at increased risk of methaemoglobinaemia, due to their thin skin, low concentrations of methaemoglobin reductase in their blood, slow metabolism of lignocaine and prilocaine. Fetal haemoglobin is more readily oxidised to methaemoglobin than is adult haemoglobin.

We obtained ethical committee approval for a randomised, double blind trial of EMLA v placebo cream in newborn babies. Parents were warned verbally and in writing of the risks of methaemoglobinaemia and advised about our methods of ensuring safe use. Fully informed verbal and written consent was obtained. Exclusion criteria were clinically apparent anaemia, oxygen treatment, cyanotic congenital heart disease, weight of less than 1500 g or a baby taking aniline derivatives.

We restricted the dose of EMLA or placebo to 0.1 ml/kg/bodyweight applied once only to an area of skin measuring 2×1 cm for exactly one hour. Each baby was watched closely for 12 hours for signs of colour change or desaturation, if necessary using a pulse oximeter or other monitors. Blood tests for methaemoglobin, lignocaine, prilocaine and methaemoglobin reductase concentrations

were available, and intravenous methylene blue, the antidote, was to hand.

Our trial was abandoned after 22 infants had been entered. Obtaining fully informed consent was usually difficult due to mothers' fears of methaemoglobinemia and lack of reports of the safety of EMLA in neonates, so recruitment was too slow to complete the trial within a reasonable length of time. Randomisation had resulted in five babies given EMLA and 17 placebo.

No baby who received EMLA became blue, desaturated, or developed symptoms, so five neonates were treated safely with EMLA on our fairly stringent regimen. We would be interested to know how the Edinburgh team coped with explaining and countering the possible hazards of methaemoglobinemia which do not seem well researched in neonates. Knowledge of the safe use of EMLA in their 28 neonates as well as our precautions in five babies, and Koren's suggestions of unofficial safe use should greatly facilitate obtaining informed consent in future trials.

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- 1 McIntosh N, van Veen L, Brameyer H. Alleviation of heel prick in preterm neonates. *Arch Dis Child* 1994; 70: F177-81.
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Dr McIntosh comments:

In our studies using EMLA cream we were attempting to reduce pain and distress (apparently unsuccessfully) in newborn infants receiving heel pricks. The parents were informed that EMLA cream had not been used other than in our own study on neonates, but that it was commonly used and with no problem in older children. We knew about the possibility of methaemoglobinemia but at the time of starting the study there was only one report of this problem in a child who was also receiving a sulphonamide, so we did not believe that we ought to inform the parents of this specific but theoretical hazard.

Lipid peroxidation as a measure of oxygen free radical damage in the very low birthweight infant

EDITOR,—We read with interest the paper by Inder *et al* on lipid peroxidation as a measure of oxygen free radical damage in preterm infants.¹ They showed a rise in malondialdehyde detected by the thiobarbituric acid (TBA) test over the first week which was significantly greater in those infants developing chronic lung disease. We have also used the TBA test to detect lipid peroxidation in 131 very preterm infants during the first seven days after birth. Concentrations rose from a median of 2.13 $\mu\text{mol/l}$ (1.63-2.77 range) on day 1 to 3.27 $\mu\text{mol/l}$ (2.49-4.48) on day 7 in those not developing chronic lung disease and from 2.07 $\mu\text{mol/l}$ (1.16-2.98) to 3.77 $\mu\text{mol/l}$ (2.6-4.21) in the 40 infants who developed chronic lung disease. No significant difference was observed. It is of interest that our values for the TBA test were about 30 times lower than those of Inder *et al*, in keeping with other published values for the test.² We used a fluorimetric method, but the HPLC technique used by Inder *et al* generally gives lower values than the fluorimetric method.³ Until these differences are explained, we cannot accept the authors' findings as evidence for lipid peroxidation in very preterm infants.

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Dr Inder and coauthors comment:

We are grateful for the query from Professor Cooke and colleagues which identified an unfortunate calculation error in our malondialdehyde-thiobarbituric acid (MDA-TBA) values that occurred during the conversion of

our standard values in ng/ml to $\mu\text{mol/l}$. Due to this error the published MDA-TBA values were too high by a factor of 60, and should read for cord blood in full term infants ($n=48$) mean (SD) 1.05 $\mu\text{mol/l}$ (0.16); premature infants without chronic lung disease ($n=6$) from cord blood concentrations of 1.19 (0.1) $\mu\text{mol/l}$ to 1.72 (0.1) $\mu\text{mol/l}$ at 7 days and in premature infants with chronic lung disease ($n=16$) from cord blood concentrations of 1.42 (0.1) $\mu\text{mol/l}$ to 2.66 (0.2) $\mu\text{mol/l}$ at 7 days. These values are approximately half those found by Cooke *et al* in his premature infants. However, the significance of the raised MDA-TBA values in premature infants with chronic lung disease is unchanged. Why did our assay detect a significant difference in MDA-TBA concentrations? The key issue relates to the specificity of thiobarbituric assays for malondialdehyde as indicators of lipid peroxidation. Both the method we used¹ and the method of Wong *et al*,² use HPLC to measure MDA-TBA, which eliminates inaccuracies due to interfering chromogens. However, there are several important differences. In our assay, no EDTA is added, plasma lipids are extracted before analysis, and ferric chloride (FeCl_3) plus butylated hydroxytoluene are added before heating with TBA. The rationale for adding FeCl_3 was to promote efficient breakdown of lipid hydroperoxides to MDA,³ but we are not sure that this is its only mode of action. The Wong method uses whole plasma and is thought to measure primarily protein bound MDA. Thus, although both are considered to be indicators of lipid peroxidation the two methods may clearly be measuring two different parameters. Further ongoing research in our premature infants continues to support the findings we have published. However, to understand the true nature of the MDA-TBA product measured, more specific analytical measures of lipid peroxidation products are awaited.

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